Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Global CNS Depression	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	**Onset:** • 1–6 days after starting LPV/r **Presentation** *Neonates/Premature Infants:* • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)	Unknown; rare case reports have been published	Prematurity Low birth weight Aged <14 days (whether birth was premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of ≥14 days unless no other alternatives are available, see Lopinavir/Ritonavir.	Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once the patient is outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	**Onset:** • For many symptoms, onset is 1–2 days after starting EFV. • Many symptoms subside or diminish by 2–4 weeks, but symptoms may persist in a significant proportion of patients. **Presentation (May Include One or More of the Following)** *Neuropsychiatric Symptoms:* • Abnormal dreams • Psychosis • Suicidal ideation or attempted/ completed suicide *Other CNS Manifestations:* • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration • Seizures (including absence seizures) • Cerebellar dysfunction (e.g., tremor, dysmetria, ataxia) **Note:** CNS side effects (e.g., impaired concentration, abnormal dreams, sleep disturbances) may be more difficult to assess in children.	Variable, depending on age, symptoms, and assessment method **Children:** • 24% of patients experienced any EFV-related CNS manifestation in one case series, with 18% of participants requiring drug discontinuation. • Five of 45 participants (11%) experienced new-onset seizures in one study of children aged <36 months; two of these participants had alternative causes for seizures. • Cases of cerebellar dysfunction have been reported in children with very high EFV plasma levels. **Adults:** • 30% incidence for any CNS manifestations of any severity. • 6% incidence for EFV-related, severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality. • One case series reported 20 women with ataxia that resolved upon EFV discontinuation, but frequency was not reported.	Insomnia is associated with elevated EFV trough concentration (≥4 mcg/mL) CYP2B6 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 T/T genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants) History of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. Prescreen for psychiatric illness; avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs. Consider using TDM in children with mild or moderate EFV-associated toxicities.	If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration is >4 mcg/mL and/or symptoms are severe, strongly consider drug substitution if a suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with input from an expert pharmacologist).

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	RPV	**Onset:** • Most symptoms occur in the first 4–8 weeks of treatment. **Presentation** *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares *Other CNS Manifestations:* • Headache • Dizziness • Insomnia • Somnolence	**Adults:** • CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (most were Grade 1). Depressive disorders of all severity grades were reported in 9% of patients; 1% of patients discontinued RPV due to severe depressive disorders. **Children:** • Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including one suicide attempt. • Somnolence was reported in five of 36 children (14%).	History of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in cases of severe symptoms.
	RAL	**Onset:** • As early as 3–4 days after starting RAL **Presentation:** • Increased psychomotor activity • Headaches • Insomnia • Depression • Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)	**Children:** • Increased psychomotor activity was reported in one child. **Adults:** • Headache • Insomnia (<5% in adult trials) • Rare case reports of cerebellar dysfunction in adults	Elevated RAL concentrations Co-treatment with TDF, a PPI, or inhibitors of UGT1A1 Prior history of insomnia or depression	Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.	Consider drug substitution (RAL or coadministered drug) in cases of severe insomnia or other neuropsychiatric symptoms.

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	DTG	**Onset:** • 7–30 days after starting DTG **Presentation** *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation or attempted/ completed suicide • Drowsiness • Neurocognitive deficits (lower total competence and school performance) *Other CNS Manifestations (Generally Mild):* • Sleep disturbances • Dizziness • Headache	**Children:** • In a retrospective cohort analysis, neuropsychiatric events that resulted in discontinuation occurred in two of 29 (6.8%) children who initiated DTG. **Adults:** • 2.7% of the neuropsychiatric AEs reported in a large prospective cohort resulted in treatment discontinuation. • Higher frequency of neuropsychiatric symptoms reported with DTG than with other INSTIs. A class effect has been suggested.	Pre-existing depression or other psychiatric illness History of ARV-related neuropsychiatric symptoms Higher frequency of neuropsychiatric symptoms reported when DTG is coadministered with ABC; however, evidence is conflicting. UGT1A1*6 and/or *28 polymorphism (reported in patients of Asian descent)	Use with caution in the presence of psychiatric illness, especially in patients with depression or a history of ARV-related neuropsychiatric symptoms. Consider morning dosing of DTG.	For persistent or severe neuropsychiatric symptoms, consider discontinuing DTG if a suitable alternative exists. For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.

Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 14, 2020; last reviewed April 14, 2020) (page 4 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	BIC	**Onset:** • 1–63 days after starting BIC (as late as 233 days for schizoaffective disorders) **Presentation** *Neuropsychiatric Symptoms:* • Depression or exacerbation of pre-existing depression • Suicidal ideation or attempted suicide • Schizoaffective disorders • Anxiety *Other CNS Manifestations (Generally Mild):* • Abnormal dreams • Dizziness • Insomnia	Data in children and adults come mostly from clinical trials. Overall, the frequency of neuropsychiatric events in BIC and DTG comparator arms appeared similar in adult clinical trials. **Children:** • 1 child (1%) had Grade 2 insomnia and anxiety that led to drug discontinuation. **Adults:** • Abnormal dreams, dizziness, and insomnia occurred in 1% to 5% of adults. • Suicidal ideation, suicide attempts, schizoaffective disorders, and depression occurred in <1% of adults.	Pre-existing depression or other psychiatric conditions History of ARV-related neuropsychiatric symptoms	Use with caution in the presence of psychiatric conditions, or in patients with a history of ARV-related neuropsychiatric symptoms.	For persistent or severe neuropsychiatric symptoms, consider discontinuing BIC if a suitable alternative exists. For mild symptoms, continue BIC and counsel patient that symptoms will likely resolve with time.

Key: ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; UGT = uridine diphosphate-glucuronosyltransferase

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